Paper No. 44

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOHN P. ATKINSON,
DENNIS HOURCADE, and
MALGORZATA KRYCH

Appeal No. 2001-1039
Application No. 08/126,505

ON BRIEF

Before WILLIAM F. SMTIH, SCHEINER, and ADAMS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 3, 8, 9, 12, 13, 15, 16, 18, 23, 24, 27, 28, and 30 through 32. Claims 4, 5, 10, 11, 14, 19, 20, 25, 26, 29, and 34 are pending but have been withdrawn from consideration by the examiner.

Claims 1 and 8 are representative of the subject matter on appeal and read as follows:

1. An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and those complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein said protein analog is selected from the group consisting of complement regulating protein analogs containing short consensus repeats derived from a second, different complement regulating protein not including combinations consisting of complement receptor 1 and complement receptor 2 complement regulating protein analogs wherein the short consensus repeats are rearranged, and complement regulating protein analogs consisting of as few as three short consensus repeats wherein the protein analog binds C3b, C4b or C3b and C4b.

8. An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2)(Sequence ID Nos 1 and 3) replaced with CR1 amino acids 497-618 (SCR 8-9)(Sequence ID Nos. 2 and 4) and CR1-4(8,9) with deletion of 194-253; and substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K (Sequence ID No. 11), or these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G.

The references relied upon by the examiner are:

Bell et al. (Bell)	4,935,233	Jun. 19, 1990
Fearon et al. (Fearon)	5,256,642	Oct. 26, 1993

Atkinson et al. (Atkinson), "Separation of self from non-self in the complement system," Immunology Today, Vol. 8, pp. 212-215, Ref. 1-AT (1987)

Lowell et al. (Lowell), "Mapping of the Epstein-Barr virus and C3dg binding sites to a common domain on complement receptor type 2," J. Experimental Medicine, Vol. 170, pp. 1931-46 (December 1989)

Caras et al. (Caras) (PCT Application)	WO 89/01041	Feb. 9, 1989

Claims 8, 9, 23, and 24 stand rejected 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1, 3, 12, 13, 15, 16, 18, 27, 28, and 30 through 32 stand rejected under 35 U.S.C. § 103(a). The examiner relies upon Lowell, Fearon, Caras, Atkinson, and Bell as evidence of obviousness. We affirm the indefiniteness rejection and reverse the obviousness rejection.

Background

The complement system is part of the immune system which aids in the removal of foreign substances and immune complexes from animal hosts. Specification, page 1. The complement system is regulated by way of a number of interrelated mechanisms. Id., page 2. A family of proteins designated "regulators of complement activation" (RCA) are involved in regulating the complement system. In relevant part, RCA proteins include CR1, MCP, DAF, C4bp, Factor H, and CR2. Id., page 3. The cDNAs corresponding to these six proteins have been obtained and sequenced. Id., page 4. Appellants describe these six proteins further, stating:

> There is considerable uniformity among the RCA family of proteins. All of them are composed of 60-70 amino acid repeating units commonly designated "short consensus repeats" (SCRs). Each SCR shares a number of invariant or highly conserved amino acid residues with other SCRs in the same protein or SCRs in other family members. Those members of the family which are membrane bound also have at their C termini either transmembrane regions and intracellular regions or a glycolipid anchor.
>
> The SCRs form the extracellular portions of those members of the family which are membrane-bound and almost all of the protein structure in the secreted members. Two covalently-crosslinked cysteine pairs establish two loops within each SCR. The smallest family members are DAF and MCP; each contains four SCRs followed by an 0-linked glycosylation region. DAF is terminated with a glycolipid anchor while MCP ends with an extracytoplasmic segment of unknown significance, a transmembrane region and an intracellular domain. Of the secreted

> members of the family, factor H contains twenty SCRs, while the native form of C4bp is an association of seven subunits of eight SCRs (the C4bp alpha chains) and one subunit of three SCRs (the C4bp beta chain). Both C4bp chains conclude with non-SCR domains that interconnect the chains through disulfide linkages. CR2 contains sixteen SCRs, a transmembrane region and an intracellular domain. The most common polymorphic form of CR1 contains four repeating units of seven similar SCRs (long homologous repeats or LHRS) numbered 1-28, followed by an additional two SCRs designated 29 and 30, a transmembrane region and an intracellular region.

Specification, page 4, line 22 - page 5, line 20.

The present invention is explained by appellants as follows:

> Analogs of RCA-encoded proteins which are modified full-length or truncated forms of these regulatory proteins are described and demonstrated to inhibit complement. These analogs include RCA proteins having site-specific mutations, RCA protein hybrids which contain one or more SCRs from more than one RCA protein, modifications of RCA recombinants in which SCRs are arranged in different orders, and truncated versions of RCA proteins containing as few [sic] three SCRs. The modified proteins retain complement inhibitory activity, which may be altered in specificity, affinity, or mechanism.

Specification, page 9, lines 20 - 31.

Discussion

As an initial matter, we must determine what subject matter is before us for review in this appeal since the examiner has required appellants to elect species for examination on the merits. In Paper No. 8, entered June 14, 1994, the examiner required restriction between two groups of claims and depending upon the group of claims elected, election of species from two different groups. Paper No. 8, pages 2-3. Appellants' initial election was to prosecute the invention involving claim 1 and as the first species, the analog containing short consensus repeats derived from a second, different complement regulating protein, and as the second species, the protein is CR1.

Id., page 4. According to the examiner's action set forth in Paper 13 (May 15, 1995), appellants confirmed their election of CR1 but did not affirm their provisional election of species of analog proteins containing short consensus repeats derived from the second, different complement regulating protein but, rather, appellants then elected the species of analog having defined amino acid substitutions. The examination proceeded on that basis.

Claims 8, 9, 23, and 24 were the claims directed to the newly elected subject matter and examined on the merits by the examiner. See, e.g., Paper No. 18 (April 3, 1996). The examiner determined in Paper No. 24 (January 27, 1997):

> Claims 8-9 and 23-24 have been examined and are free of the prior art. There are no claims that are generic to these species. However, as indicated in Paper No. 21, page 4, subject matter that was examined in Paper No. 8 will be rejoined and examined with claims 8-9 and 23-24. In that Office action, a species election of an analog containing SCR domains from a different RCA protein was elected with a further election being that the species analog protein is CR1 (Paper No. 8, page 4). Claims 1, 3, 12-13, 15-16, 18, 27-28 and 30-32 are generic and will be examined only insofar as they read on an analog of CR1 containing SCR domains from a different protein. There are no species claims. Claims 4-5, 10-11, 14, 19-20, 25-26, 29 and 34 are withdrawn from further reconsideration by the Examiner, 37 C.F.R. 1.142(b), as being drawn to non-elected species.

From this, it is apparent that claim 1 on appeal has only been examined to the extent that it reads on an analog of CR1 containing short consensus repeats derived from a second, different complement regulating protein.[1] Thus, if claim 1 on appeal was redrafted to read only on the elected subject matter, it would read as follows:

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[1] We find no discussion in the various requirements to elect species of that portion of claim 1 directed to "those complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted." Accordingly, we will assume that this aspect of the claimed subject matter has not been examined.

An analog of complement receptor 1 wherein the complement receptor 1 protein analog contains short consensus repeats derived from a second, different complement regulating protein but not from complement receptor 2 wherein the complement receptor 1 protein analog binds C3b, C4b or C3b and C4b.

1. Obviousness.

The examiner relies upon Lowell for its description of chimeric CR1/CR2 protein analogs including one in which the first two short consensus repeats of CR2 are substituted for the first two short consensus repeats of CR1. Examiner's Answer, page 5. The examiner specifically relies upon Lowell's description of an analog denominated CR2/CR1 XE described in Figure 1, page 1936 and page 1939 of Lowell. The examiner states that Lowell does not describe that CR2/CR1 XE binds either C3b or C4b as required by claim 1. However, the examiner takes notice of appellants' so-called admission at page 5 of the present specification that the first two short consensus repeats of CR1 are required for C4b binding while the short consensus repeats 8 and 9 and possibly short consensus repeat 10 as well as short consensus repeats 15 and 16 and possibly 17 constitute two C3b binding sites. From this information, the examiner concludes that CR2/CR1 XE would "inherently bind C3b." Examiner's Answer, page 6. In the examiner's view, Lowell differs from the elected subject matter of claim 1 in that Lowell does not "teach or suggest making a chimeric RCA protein analog other than CR1/CR2, as recited in the instant claims." Id.

The examiner relies upon Caras for its disclosure that a soluble DAF can be used to inhibit complement activation in vivo for treatment of autoimmune and inflammatory diseases and Fearon for its teaching that a soluble CR1 fragment can be used to inhibit inappropriate complement activation in vivo for the treatment of such

disorders as inflammatory and autoimmune diseases. Id. The examiner also relies upon Fearon and Caras for their teachings that "ligand-binding fragments of CR1 and DAF, respectively, can be used therapeutically." Id.

Atkinson is relied upon for its teaching that RCA proteins are important in regulation of complement activation and that CR1 and DAF as well as other RCA proteins have interrelated effects in controlling the complement system. Id.

Bell is relied upon for its description of chimeric proteins formed from covalently linked polypeptide cell modulators wherein the two modulators have different activities which are complimentary to each other. Examiner's Answer, page 7.

From these teachings, the examiner concludes:

> It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the chimeric CR1/CR2 protein taught by Lowell and substitute for the CR2 SCRs the SCRs of DAF, in order to produce a chimeric protein which would have C3b binding (via CR1) and DAF activity. Furthermore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the chimeric protein taught by Lowell and make an RCA analog in which the ligand-binding SCRs or DAF are linked to the entire soluble CR1, rather than have substitution of the two N-terminal SCRs of CR2 for the two N-terminal SCRs or CR1, in order to obtain a chimeric RCA molecule which could bind C3b and C4b and have decay accelerating activity. One would be motivated to make these modifications in order to obtain a molecule which could be used therapeutically to additively inhibit complement activation through binding of C3b and/or C4b, and through its decay accelerating activities as taught by Bell. One would be motivated to make either the full-length CR1/DAF chimeric protein or CR1/DAF chimeric protein in which the first two SCRs of CR1 are missing because one would expect that administration of CR1 and DAF would have additive effects in inhibiting complement activation, and Bell teaches that administration of a chimeric protein will have the effect of the two single effectors administered separately. It also would have been obvious to one having ordinary skill in the art to make this chimeric protein using DNA encoding such a protein, expression vectors and host cells to recombinantly produce this protein, because Lowell used this method to make CR1/CR2 and because Bell teaches that chimeric proteins are

> preferably made by genetic engineering (col. 2, lines 37-44). Furthermore, one would have had a reasonable expectation of success because Lowell teaches that chimeric proteins containing the structurally and functionally similar SCR domains of CR2 were able to bind their native ligands in the CR2/CR1 chimera.

Examiner's Answer, paragraph bridging pages 7 and 8.

Appellants argue that Lowell made the chimeric proteins for an entirely different purpose, i.e., determining which regions of CR2 were critical for binding to the protein by the Epstein-Barr virus and thus Lowell did not test the functional activity of the chimeric proteins. Appeal Brief, page 9. Appellants argue that it is only they who rearranged or inserted short consensus repeats from one protein into another to determine the effect on binding to C3b, C4b or C3b and C4b. Id. Appellants also argue that the remaining references do not in combination with Lowell render the elected subject matter obvious in that Caras and Fearon do not suggest that one could use fewer short consensus repeats or rearrange the short consensus repeats or exchange the short consensus repeats between complement regulatory proteins. Id., page 10. Appellants characterize Bell as only disclosing that one can made chimeric molecules using proteins which are short with no structures for assembling short consensus repeats which have a single activity even though they bind at different receptors. Id. Finally, appellants argue:

> The proteins from which the claimed analogs are derived are very large, complex, and in most cases, have multiple biological activities. One could not have predicted that changing domains within a protein could confer a discrete activity since these are extremely large and complex proteins, and one would predict steric hindrance and other factors to interfer with the transfer of activity. It was as likely that rearranging these highly conserved domains would destroy their activities as it was likely that any one or more activities would be retained. Since Lowell did not screen for functional activity of his constructions, there was no way to predict that

> even the one construct which inserted CR1 SCRs into CR2 would have activity - only appellants ever actually tested constructs for binding.

Id., page 11.

In order to combine references under 35 U.S.C. § 103, the examiner must identify a reason, suggestion, or motivation whereby a person of ordinary skill in the art would make the substitutions required. That knowledge must come from the prior art, not applicants' disclosure of the invention itself. In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Here, the examiner has proposed two specific modifications of Lowell, each of which include the use of short consensus repeats of DAF, so that the resulting modified CR1 protein would have C3b binding or C3b and C4b binding and DAF activity. However, in our view, a reading of Lowell does not support the examiner's proposed substitutions.

The end result of each of the examiner's proposed substitutions is the obtention of a therapeutic protein. Lowell is not interested in obtaining such a protein but, rather, is interested in only determining binding sites. While certain of the references the examiner relies upon are involved with therapeutic proteins, the examiner has not identified specific teachings in the references which suggest the creation of analog proteins from the RCA family.[1] The chimeric proteins of Bell are not stated to include proteins from the RCA family and the examiner has not adequately explained on this record why the teachings of Bell would suggest the substitutions needed in Lowell in order to arrive at the elected subject matter.

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[1] We note that Fearon does discuss CR1 analogs, e.g., column 24, line 15 - column 25, line 63, but the examiner has not considered these disclosures explicitly in making her rejection under 35 U.S.C. § 103.

On this record, we are constrained to conclude that the examiner's conclusions in regard to obviousness are based upon inappropriate hindsight based upon knowledge gleaned from the disclosure of the present invention instead of the teachings of the applied references.

We reverse the obviousness rejection.

2. Claim definiteness.

Claims 8, 9, 23, and 24 have been determined by the examiner to be indefinite for a very specific reason, i.e., "it is not clear whether all instances of a given residue are to be substituted, i.e. wither [sic] all "I" residues are replaced by either L or V, or only some of the I residues, or only a single I residue, and if so, which one." Examiner's Answer, page 4. Appellants' arguments in the Appeal Brief in regard to this rejection do not acknowledge the specific reasons the examiner gives for this rejection. See Appeal Brief, pages 12-13. The examiner has identified a plausible ambiguity in the claims. It is appellants' responsibility then to argue the specifics of the examiner's position. This has not happened.

An ambiguous claim is indefinite under 35 U.S.C. § 112, second paragraph. In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Appellants have not directly argued the propriety of the rejection as made in the Examiner's Answer. Under these circumstances we will affirm the examiner's rejection under 35 U.S.C. § 112, second paragraph.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

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